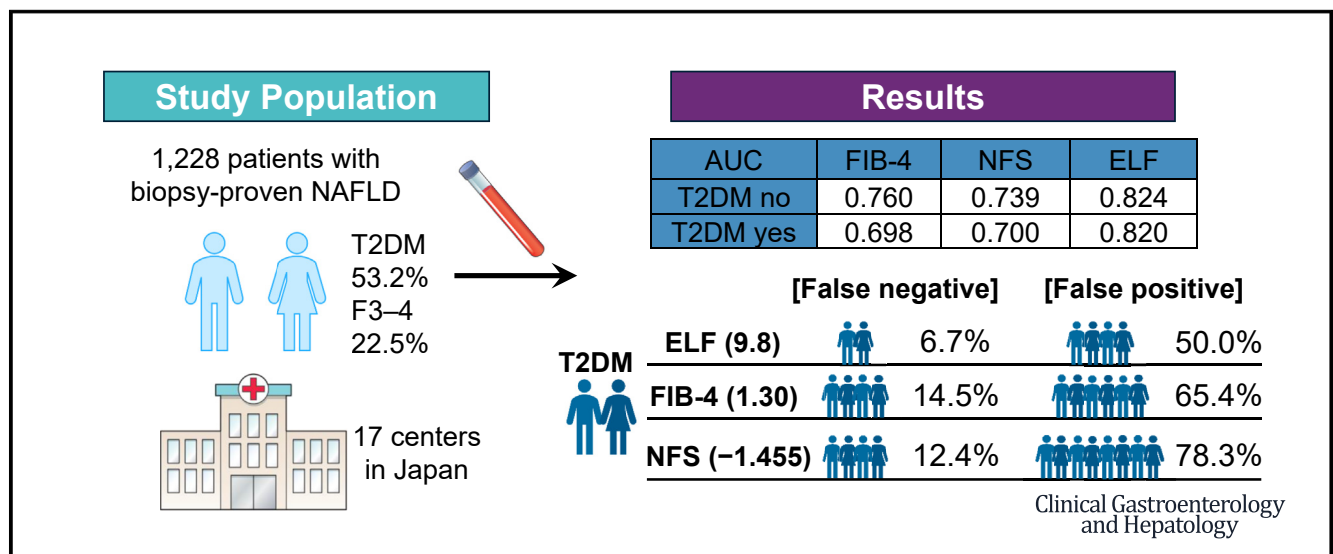




Accuracy of the Enhanced Liver Fibrosis Test in Patients With Type 2 Diabetes Mellitus and Its Clinical Implications

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Abbreviations used in this paper: AUC, area under the curve; BMI, body mass index; ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis-4; IQR, inter-quartile range; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; NIT, noninvasive test; PSM, propensity score matching; T2DM, type 2 diabetes mellitus.



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BACKGROUND AND AIMS:

The diagnostic performance of the Fibrosis-4 (FIB-4) index and nonalcoholic fatty liver disease (NAFLD) fibrosis score (NFS) is poor in patients with type 2 diabetes mellitus (T2DM). We determined the usefulness of the Enhanced Liver Fibrosis (ELF) test in patients with T2DM.

METHODS:

A total of 1228 patients with biopsy-proven NAFLD were enrolled. The diagnostic performance of the ELF test for predicting advanced fibrosis in participants with or without T2DM was evaluated in comparison with the FIB-4 index and NFS.

RESULTS:

Overall, the area under the curve of the ELF test for predicting advanced fibrosis was greater (0.828) than that of the FIB-4 index (0.727) and NFS (0.733). The diagnostic performance of the ELF test (area under the curve, 0.820) was also superior to that of the FIB-4 index (0.698) and NFS (0.700) in patients with T2DM. With the low cutoff values for each noninvasive test, the ELF test provided an acceptable false negative rate (cutoff value 9.8, 6.7%) in this population, unlike the FIB-4 index (1.30, 14.5%) and NFS (−1.455, 12.4%). After propensity score matching to avoid selection bias including age, sex, body mass index, and the prevalence of advanced fibrosis, the ELF test with a low cutoff value showed a high sensitivity ($\geq 91.4\%$) and a high negative predictive value ($\geq 96.8\%$), irrespective of the presence or absence of T2DM.

CONCLUSIONS:

The high diagnostic performance of the ELF test for predicting advanced fibrosis in individuals with or without T2DM could address an unmet medical need for accurate assessment of liver fibrosis in patients with diabetes and NAFLD.

Keywords: NAFLD; Fibrosis; Noninvasive Tests; ELF; Diabetes.

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease, with a global morbidity of approximately 25%.¹ NAFLD can progress and eventually lead to liver cirrhosis and hepatocellular carcinoma, along with the deterioration of liver fibrosis. This fibrosis is the most critical liver-related prognostic factor in patients with NAFLD²; therefore, assessing the degree of liver fibrosis in patients with NAFLD is of great clinical importance. Although liver biopsy is the gold standard for diagnosis and staging of liver fibrosis in NAFLD, it has several drawbacks, such as sampling error, cost/effort, the risk of complications, and observer variation in pathologic assessment.

The usefulness of the Fibrosis-4 (FIB-4) index^{3–5} and NAFLD fibrosis score (NFS)⁶ as noninvasive alternatives to liver biopsy has been established, and these measurements are recommended in NAFLD practice guidelines.^{7–9} However, the diagnostic performance of the FIB-4 index and NFS is poor in patients with type 2 diabetes mellitus (T2DM).^{10–13} Considering that T2DM is a well-known risk factor for the progression of liver fibrosis and the development of hepatocellular carcinoma in patients with NAFLD,^{14,15} the poor diagnostic performance of the FIB-4 index and NFS in these high-risk patients is a major clinical problem. Imaging techniques such as magnetic resonance elastography and transient elastography, which provide excellent performance and complementary diagnosis in fibrosis evaluation, are not widely available in the diabetes primary care setting. Therefore, the development of a reliable alternative serum-based biomarker to the FIB-4 index and NFS for accessing liver fibrosis in patients with diabetes and NAFLD is urgently needed.

The Enhanced Liver Fibrosis (ELF) test is a serum biomarker consisting of 3 matrix turnover proteins: hyaluronic acid, procollagen III amino-terminal peptide, and tissue inhibitor of matrix metalloproteinase 1.¹⁶ The high clinical usefulness of the ELF test in NAFLD practice has been confirmed by several studies.^{17–19} In observational studies, the performance of the ELF test was unaffected by the presence or absence of T2DM.^{20,21} Thus, the ELF test could address an unmet medical need to accurately screen for advanced fibrosis in patients with diabetes and NAFLD. In addition, the diagnostic performance of the ELF test may also vary by age, sex, and body mass index (BMI),²² which has not been well characterized.

We characterized the diagnostic performance of the ELF test according to patient background, compared with that of the FIB-4 index and NFS in a large cohort of Japanese patients with biopsy-proven NAFLD.

Materials and Methods

Study Design and Patients

This retrospective, multicenter study was part of research focused on noninvasive tests (NITs) conducted by a multi-institutional joint research group called the Japan Study Group of NAFLD. A total of 1228 patients with biopsy-proven NAFLD who did not meet the exclusion criteria were enrolled in this study. Exclusion criteria are detailed in the [Supplementary Methods](#).

This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the institutional review board of each participating institution.

Clinical and Laboratory Evaluation

Clinical evaluations and laboratory data were collected at the time of liver biopsy ([Supplementary Methods](#)). Patients were diagnosed with T2DM according to the American Diabetes Association clinical practice recommendations,²³ as detailed in the [Supplementary Methods](#). The FIB-4 index³ and NFS⁶ were calculated as reported previously. The ELF test was performed using frozen serum samples collected at the time of liver biopsy. Two cutoff values (high and low), which are well validated for each marker, were used in this study: FIB-4 index (1.30 and 2.67),⁵ NFS (−1.455 and 0.676),⁶ and ELF test (9.8 and 11.3).²² Of the 1228 biopsy-proven NAFLD patients, 657 underwent liver stiffness measurement (LSM) evaluation by FibroScan 430, 502, or 530 (Echosens, Paris, France) within 3 months before and after liver biopsy. For LSM, a low cutoff value of 8.0 kPa and a high cutoff value of 12.0 kPa were used in this study.⁸

Histopathological Evaluation

Liver biopsy was performed under ultrasound guidance using a 16-gauge biopsy needle. Liver specimens stained with hematoxylin and eosin and Masson trichrome were centrally reviewed using Nonalcoholic Steatohepatitis Clinical Research Network criteria²⁴ by an experienced pathologist (S.A.) specializing in liver pathology at Saga University who was blinded to the patients' data.

Statistical Analyses

Continuous variables are presented as medians and interquartile ranges (IQRs), while categorical variables are presented as numbers and percentages. Continuous variables with skewed distributions were compared between 2 groups using the Mann-Whitney *U* test, while categorical variables were compared using the Fisher exact test. Multiple logistic regression analysis was used to identify the independent factors that were significantly associated with concordance between the ELF test (cutoff value 9.8) and liver fibrosis. The diagnostic performance of NITs for predicting advanced fibrosis was evaluated using the receiver-operating characteristic curve and compared using the DeLong test. Propensity score matching (PSM) was performed to reduce differences in baseline characteristics between patients with and without T2DM ([Supplementary Methods](#)). A decision tree algorithm was constructed to reveal profiles associated with advanced fibrosis using the following factors:

What You Need to Know

Background

Accurate noninvasive tests for liver fibrosis in patients with type 2 diabetes mellitus are urgently needed.

Findings

The Enhanced Liver Fibrosis test provided accurate and reliable diagnostic performance for predicting advanced fibrosis in patients with nonalcoholic fatty liver disease (NAFLD) with or without type 2 diabetes mellitus in comparison with the Fibrosis-4 index and NAFLD fibrosis score.

Implications for patient care

An algorithm for liver fibrosis assessment using the Enhanced Liver Fibrosis test is recommended, especially in patients with type 2 diabetes mellitus in whom the diagnostic performance of the Fibrosis-4 index and NAFLD fibrosis score is unacceptably poor.

age, sex, BMI, T2DM, FIB-4 index (cutoff value 1.30), NFS (cutoff value −1.455), and ELF test (cutoff value 9.8). Decision tree analysis was performed using R software (version 4.3.1; R Foundation for Statistical Computing), and all other statistical analyses were performed using IBM SPSS version 17.0 (IBM Japan, Tokyo, Japan). The level of statistical significance was set at $P < .05$.

Results

Patient Characteristics

The baseline characteristics of the 1228 patients with NAFLD are shown in [Table 1](#). There were 559 males and 669 females, with a median age of 60 years (IQR, 47–67 years) and a median BMI of 27.5 kg/m² (IQR, 24.9–30.7 kg/m²). Patients were categorized as normal weight/underweight (BMI <25 kg/m²), overweight (BMI ≥25 kg/m² but <30 kg/m²), or obese (BMI ≥30 kg/m²) as follows: 310 (25.2%), 554 (45.1%), and 364 (29.6%), respectively. The prevalence of T2DM was 53.2% ($n = 653$ of 1228). Advanced fibrosis (fibrosis stage 3–4) was present in 276 (22.5%) patients.

Overall

Using receiver-operating characteristic analyses for the diagnosis of advanced fibrosis, the area under the curves (AUCs) of the NITs were as follows: FIB-4 index (0.727), NFS (0.733), and ELF test (0.828) ([Table 2](#)). The AUC of the ELF test was superior to that of the FIB-4 index ($P < .001$) and NFS ($P < .001$). When using low cutoff values for each NIT, the ELF test (cutoff value 9.8)

Table 1. Baseline Characteristics of the 1228 Patients With Nonalcoholic Fatty Liver Disease

Age, y	60 (47 to 67)
Sex	
Female	669 (54.5)
Male	559 (45.5)
Body weight, kg	70.4 (61.0 to 80.7)
BMI, kg/m ²	27.5 (24.9 to 30.7)
Normal weight/underweight (<25 kg/m ²)	310 (25.2)
Overweight (≥25 kg/m ² but <30 kg/m ²)	554 (45.1)
Obese (≥30 kg/m ²)	364 (29.6)
Platelets (×10 ³ /μL)	203 (164 to 247)
AST, U/L	48 (34 to 70)
ALT, U/L	61 (39 to 95)
γ-GTP, U/L	60 (38 to 98)
ALP, U/L	86 (69 to 110)
Albumin, g/dL	4.3 (4.0 to 4.5)
Total cholesterol, mg/dL	192 (171 to 218)
LDL cholesterol, mg/dL	120 (99 to 142)
HDL cholesterol, mg/dL	46 (40 to 55)
Triglyceride, mg/dL	136 (98 to 185)
Plasma glucose, mg/dL	107 (96 to 128)
HbA1c, %	6.0 (5.6 to 6.8)
T2DM	
No	575 (46.8)
Yes	653 (53.2)
FIB-4 index	1.82 (1.08 to 2.86)
NFS	−0.743 (−1.772 to 0.405)
ELF test	9.9 (9.2 to 10.8)
Fibrosis stage	
0	214 (17.4)
1	411 (33.5)
2	327 (26.6)
3	237 (19.3)
4	39 (3.2)
Fibrosis stage	
0–2	952 (77.5)
3–4	276 (22.5)

Values are median (interquartile range) or n (%).

γ-GTP, gamma glutamyl transpeptidase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BMI, body mass index; ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis-4; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; T2DM, type 2 diabetes mellitus.

showed high sensitivity (92.4%) and specificity (54.5%) compared with the FIB-4 index (cutoff value 1.30; 85.9% for sensitivity and 39.3% for specificity) and NFS (cutoff value −1.455; 85.1% for sensitivity and 36.3% for specificity) (Figure 1). Multiple logistic regression

analysis showed that an age of <65 years ($P < .001$; odds ratio, 2.13; 95% confidence interval, 1.66–2.74) and male sex ($P < .01$; odds ratio, 1.41; 95% confidence interval, 1.11–1.80) were independent factors for concordance between the ELF test using a low cutoff value of 9.8 and liver fibrosis (Supplementary Table 1). The ELF test showed a high diagnostic ability to predict advanced fibrosis in normal weight/underweight (AUC, 0.818), overweight (AUC, 0.826), and obese (AUC, 0.838) categories (Supplementary Figure 1).

Subgroup Analysis by Age and Sex

The diagnostic performance of each NIT according to age, sex, and T2DM status is shown in Table 2. Age and sex appeared to affect the AUC of the ELF test for detecting advanced fibrosis. That is, the diagnostic performance of the ELF test was lower in patients ≥65 years of age (AUC, 0.771) than in those <65 years of age (AUC, 0.847), and lower in females (AUC, 0.805) than males (AUC, 0.854). Especially in patients ≥65 years of age, the diagnostic performance of the ELF test was reduced to the same level as that of the FIB-4 index ($P = .07$) and NFS ($P = .47$). By age and sex, the ELF test had the best predictive ability for males <65 years of age (AUC, 0.865), while the predictive ability of the test for females ≥65 years of age (AUC, 0.751) was as low as that of the FIB-4 index ($P = .54$) and NFS ($P = .68$) (Supplementary Figure 2). The diagnostic accuracy of each NIT at low cutoff values by age and sex is shown in Supplementary Figure 3. Age and sex influenced the specificity of each NIT, with a marked decrease especially in patients ≥65 years of age compared with the findings in those <65 years of age. In particular, the specificity of the FIB-4 index and NFS for patients ≥65 years of age was unacceptably poor, at 5.8% and 8.5%, respectively.

Diagnostic Performance of the NITs With or Without T2DM

For patients with T2DM, the diagnostic ability to predict advanced fibrosis was poor with the FIB-4 index (AUCs of 0.698 and 0.760 for patients with and without T2DM, respectively) and NFS (AUCs of 0.700 and 0.739 for patients with and without T2DM, respectively). By contrast, the diagnostic performance of the ELF test (AUCs of 0.820 and 0.824 for patients with and without T2DM, respectively) was more accurate and superior to that of the FIB-4 index and NFS regardless of T2DM status (Table 2). When using a low cutoff value of 9.8 in patients with T2DM, the ELF test provided an acceptable false negative rate ($n = 13$ of 193 [6.7%]) and false positive rate ($n = 230$ of 460 [50.0%]) to be used as a triaging tool for reducing unnecessary referrals without missing advanced fibrosis (Figure 2). By contrast, both false negative rates (14.5% for FIB-4 index and 12.4% for NFS) and false positive rates (65.4% for FIB-4 index

Table 2. Diagnostic Performance of the FIB-4 Index, NFS, and ELF Test

	FIB-4 Index	NFS	ELF Test	P Value	
				ELF vs FIB-4	ELF vs NFS
All patients	0.727 (0.692–0.762)	0.733 (0.697–0.770)	0.828 (0.801–0.854)	<.001	<.001
Age <65 y (n = 812)	0.708 (0.658–0.757)	0.707 (0.656–0.757)	0.847 (0.813–0.882)	<.001	<.001
Age ≥65 y (n = 416)	0.718 (0.666–0.771)	0.749 (0.696–0.801)	0.771 (0.723–0.818)	.07	.47
Male (n = 559)	0.721 (0.667–0.775)	0.721 (0.667–0.776)	0.854 (0.817–0.891)	<.001	<.001
Female (n = 669)	0.736 (0.690–0.783)	0.744 (0.696–0.792)	0.805 (0.767–0.842)	<.01	.03
T2DM no (n = 575)	0.760 (0.701–0.819)	0.739 (0.674–0.803)	0.824 (0.777–0.870)	.02	.01
T2DM yes (n = 653)	0.698 (0.652–0.744)	0.700 (0.653–0.747)	0.820 (0.785–0.854)	<.001	<.001

Values are area under the curve (95% confidence interval).
ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis-4; NFS, NAFLD fibrosis score; T2DM, type 2 diabetes mellitus.

and 78.3% for NFS) for the FIB-4 index (cutoff value 1.30) and NFS (cutoff value −1.455) in this population were unacceptably high.

PSM was performed to adjust for each group with and without T2DM by age, sex, BMI, and the prevalence of advanced fibrosis. After PSM, a matched sample consisting of 479 patients both with and without T2DM was obtained (Supplementary Table 2). In both groups, even after PSM, the ELF test showed a significantly higher AUC (0.834 and 0.809 for patients with and without T2DM, respectively) than the FIB-4 index (0.688 and 0.737 for patients with and without T2DM, respectively) and NFS (0.709 and 0.716 for patients with and without T2DM, respectively) (Table 3). The ELF test had a high sensitivity in both groups (92.9% and 91.4% with and without T2DM, respectively) and a high negative predictive value in both groups (97.3% and 96.8% with and without T2DM, respectively) when using the low cutoff value of 9.8.

Referral Strategy Using a 2-Step Algorithm Including the FIB-4 Index Followed by the ELF Test

Our decision tree analysis showed that the ELF test was the primary divergent variable for advanced fibrosis, followed by T2DM and the FIB-4 index, in that order (Supplementary Figure 4). A 2-step strategy including the FIB-4 index followed by the ELF test reduced the number of patients to be referred for further risk assessment of liver fibrosis with an acceptable false negative rate of 7.7% (Supplementary Figure 5). This strategy also reduced the number of patients undergoing the ELF test by >30% at the first-step assessment with the FIB-4 index. However, in patients ≥65 years of age, the markedly poor specificity of the FIB-4 index meant that this strategy did little to reduce the number of necessary ELF tests, and even the second step with the

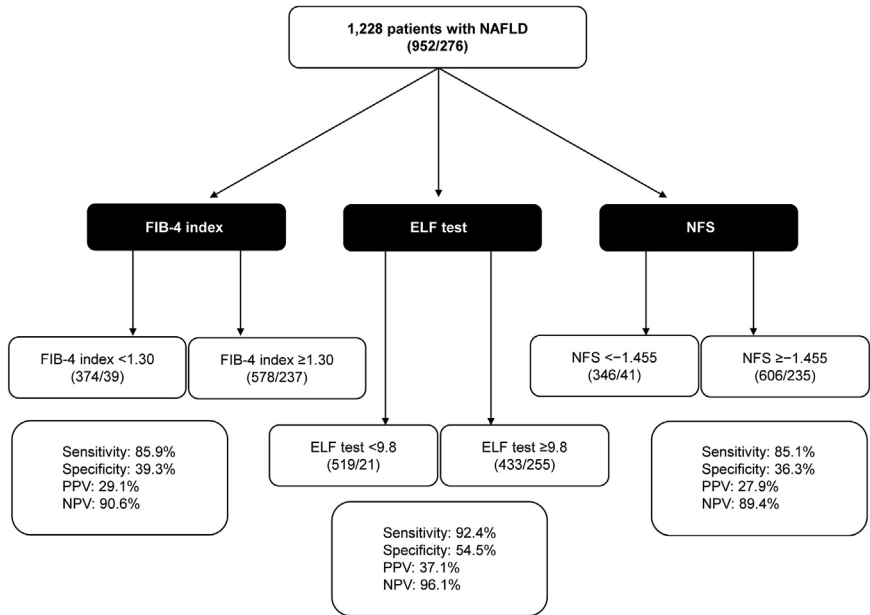


Figure 1. Diagnostic accuracy of the FIB-4 index, NFS, and ELF test for predicting advanced fibrosis (fibrosis stage 3–4) at low cutoff values. The numbers in parentheses are the number of patients without advanced fibrosis/number of patients with advanced fibrosis. NPV, negative predictive value; PPV, positive predictive value.

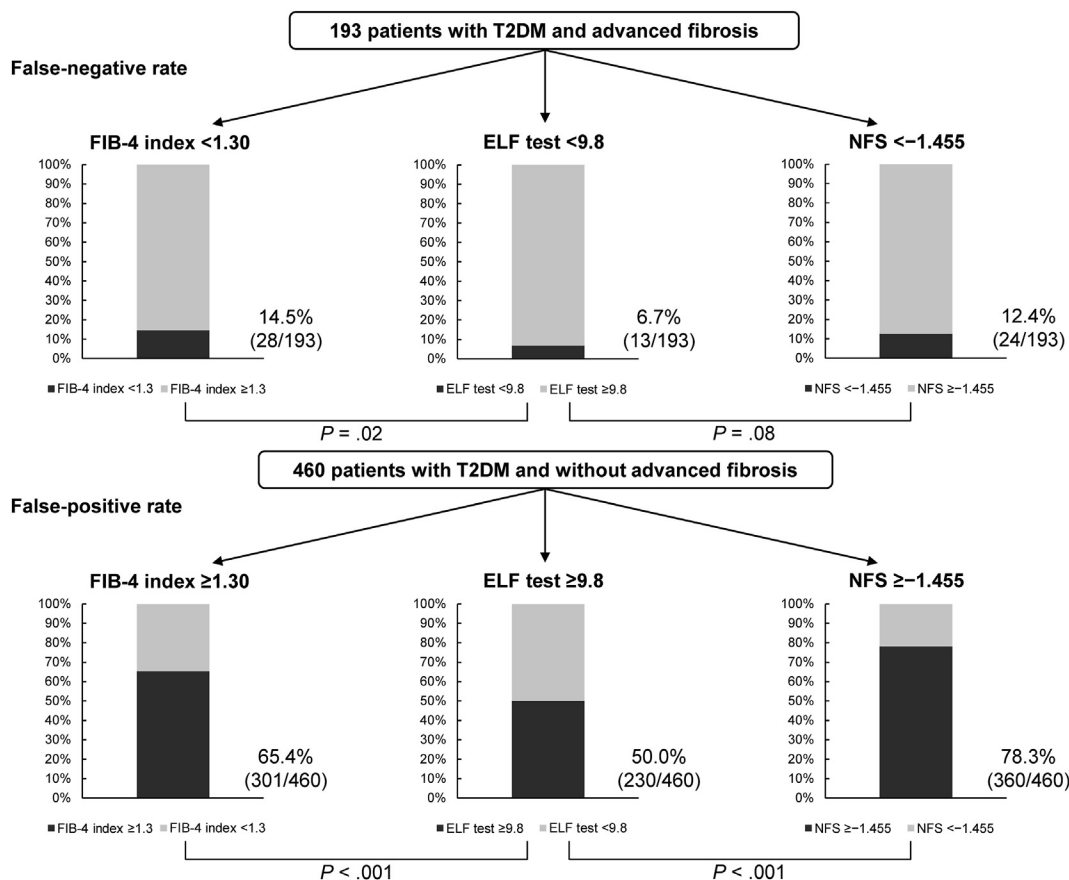


Figure 2. False negative and false positive rates of the FIB-4 index, NFS, and ELF test at low cutoff values.

ELF test did not efficiently reduce unnecessary referrals (Supplementary Figure 6). As for patients with T2DM, the high false negative rate of the FIB-4 index led to an unacceptable false negative rate of 11.3% with this strategy, suggesting a risk of missing advanced fibrosis.

Diagnostic Performance of LSM by Transient Elastography With or Without T2DM

PSM was performed in 657 patients with available data on LSM by transient elastography, yielding 246

Table 3. The Diagnostic Performance of the FIB-4 Index, NFS, and ELF Test After Propensity Score Matching

	AUC (95% CI)	Cutoff value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
FIB-4 index						
T2DM no	0.737 (0.674–0.801)	1.30	87.7	35.4	21.6	93.4
		2.67	60.5	78.1	36.0	90.7
T2DM yes	0.688 (0.617–0.758)	1.30	82.1	38.2	22.0	91.0
		2.67	50.0	78.0	32.6	88.0
NFS						
T2DM no	0.716 (0.647–0.786)	-1.455	80.2	42.2	22.0	91.3
		0.676	35.8	92.0	47.5	87.6
T2DM yes	0.709 (0.636–0.782)	-1.455	83.3	25.3	19.2	87.7
		0.676	46.4	86.6	42.4	88.4
ELF test						
T2DM no	0.809 (0.760–0.857)	9.8	91.4	52.5	28.1	96.8
	vs FIB-4: $P = .02$	11.3	37.0	91.2	46.2	87.7
	vs NFS: $P = .01$					
T2DM yes	0.834 (0.787–0.880)	9.8	92.9	53.9	30.0	96.8
	vs FIB-4: $P < .001$	11.3	40.5	93.7	57.6	87.7
	vs NFS: $P < .01$					

matched samples each for patients with and without T2DM (Supplementary Table 3). LSM had a good diagnostic ability to predict advanced fibrosis with or without T2DM (AUCs of 0.863 and 0.927 for patients with and without T2DM, respectively). When using a low cutoff value of 8.0 kPa, as with the ELF test, LSM showed a high sensitivity in both groups (93.0% and 96.2% with and without T2DM, respectively) and a high negative predictive value in both groups (95.8% and 98.3% with and without T2DM, respectively) (Supplementary Table 4).

Discussion

In this large cohort of Japanese patients with biopsy-proven NAFLD, the diagnostic performance of the ELF test (AUC, 0.828) for predicting advanced fibrosis was superior to that of the FIB-4 index (AUC, 0.727; $P < .001$) and NFS (AUC, 0.733; $P < .001$). Furthermore, the ELF test showed accurate and reliable performance with an AUC value of ≥ 0.820 , irrespective of the presence or absence of T2DM, and its superiority over the FIB-4 index and NFS was particularly marked in patients with T2DM. Even when using the low cutoff values for each NIT, the ELF test was superior to the FIB-4 index and NFS in terms of false negative and false positive rates in this population. These findings provide a rationale for using the ELF test as a first triaging tool to reduce the need for liver biopsy without missing advanced fibrosis, especially in patients with diabetes and NAFLD.

The FIB-4 index and NFS are reliable and inexpensive methods of assessing liver fibrosis, and their measurement is recommended as a first step in excluding patients with advanced fibrosis in the primary care of NAFLD.⁷⁻⁹ However, recent reports have raised concerns about the poor diagnostic performance of the FIB-4 index or NFS for detecting advanced fibrosis^{10-12,25} and fibrotic nonalcoholic steatohepatitis¹³ in patients with T2DM. In fact, in this cohort of patients with biopsy-proven NAFLD, the AUC of the FIB-4 index and NFS for predicting advanced fibrosis was also unacceptably worse in patients with T2DM (0.698 for the FIB-4 index and 0.700 for NFS) than in those without T2DM (0.760 for the FIB-4 index and 0.739 for NFS).

In this cohort, patients with T2DM were older, were more often obese, and had a higher prevalence of advanced fibrosis than those without T2DM; therefore, PSM was performed to avoid selection bias related to age, sex, BMI, and the prevalence of advanced fibrosis. After PSM, the diagnostic performance of the ELF test was similarly good in both patients without T2DM (AUC, 0.809) and with T2DM (AUC, 0.834). By contrast, even after PSM, the diagnostic performance of the FIB-4 index (AUC, 0.688) and NFS (AUC, 0.709) was inaccurate in patients with T2DM. The reasons for the poor diagnostic performance of the FIB-4 index and NFS in patients with T2DM are discussed in the Supplementary Discussion and Supplementary Table 5. With the low cutoff value

of 9.8, the ELF test had a high sensitivity in both groups (92.9% and 91.4% with and without T2DM, respectively) and a high negative predictive value in both groups (97.3% and 96.8% for patients with and without T2DM, respectively).

Although the current study had a limited sample size, the findings showed that transient elastography also had an excellent diagnostic accuracy with high sensitivity and negative predictive value at a low cutoff value of 8.0 kPa in patients with T2DM. Further studies are needed to confirm whether an algorithm involving a first-step ELF test followed by transient elastography could enhance confidence and accuracy in identifying advanced fibrosis in this population.

We evaluated the diagnostic accuracy of the 2-step strategy including the FIB-4 index followed by the ELF test, which is recommended by the American Association for the Study of Liver Diseases⁸ and the American Gastroenterological Association²⁶ for primary care settings when elastography is not available. This strategy reduced unnecessary referrals more than the ELF test alone or the FIB-4 index alone, while maintaining an acceptable false negative rate. However, for patients with T2DM, this strategy was not suitable as a triaging tool for excluding advanced fibrosis because of an unacceptable false negative rate of $>10\%$, with the result that screening for liver fibrosis with the ELF test alone (false negative rate of 6.7%) was preferable.

As with other NITs,²⁷ age and sex need to be considered when interpreting results of the ELF test.²² In particular, a large discrepancy was found between the AUCs of patients <65 years of age (AUC, 0.847) and those ≥ 65 years of age (AUC, 0.771). With low cutoff values for each NIT, the respective specificity was low in patients ≥ 65 years of age. In particular, the specificity of the FIB-4 index and NFS is known to be unacceptably low, and new thresholds for use in this population have been proposed to avoid over-referral.²⁷ As the ELF test also increases with age,²² using age-adjusted thresholds would make the ELF test even more reliable both as a first-step tool and as a second-step tool following the FIB-4 index.

This study had several limitations. First, it included only Japanese patients with NAFLD, so ethnic and racial differences may alter the results obtained. Second, the report was a retrospective, hospital-based study, which involved the potential for patient selection bias and may not be representative as applied to the real-world population for primary screening. Third, the impact of T2DM on the diagnostic performance of NITs was not fully clarified in that the study did not consider the severity of T2DM, such as glycemic control status and the use of oral hypoglycemic agents and insulin. Finally, serum-based biomarkers for liver fibrosis such as type IV collagen 7s,¹² PRO-C3 (a marker of type III collagen formation), and the ADAPT score (generated by age, platelet count, diabetes, and PRO-C3)²¹ were not available in this study.

In conclusion, this study showed that the ELF test provided accurate and reliable diagnostic performance

for predicting advanced fibrosis in patients with NAFLD with or without T2DM in comparison with the FIB-4 index and NFS. The use of the ELF test as a first step is desirable, especially in patients with T2DM in whom the diagnostic performance of the FIB-4 index and NFS is unacceptably poor.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <http://doi.org/10.1016/j.cgh.2023.11.022>.

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Hirokazu Takahashi (Conceptualization: Equal; Data curation: Lead; Formal analysis: Equal; Investigation: Equal; Methodology: Equal; Supervision: Lead; Writing – review & editing: Lead)

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Conflicts of Interest

This author discloses the following: Hideaki Fukushima is an employee of Siemens Healthcare Diagnostics K.K. The remaining authors disclose no conflicts.

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Supplementary Methods

Study Design and Patients

The main exclusion criteria were (1) <20 years of age; (2) daily alcohol consumption of >30 g for males and >20 g for females; (3) presence of other chronic liver diseases, such as viral hepatitis B or C, autoimmune hepatitis, primary biliary cholangitis, primary sclerosing cholangitis, α -1-antitrypsin deficiency-associated liver disease, Wilson's disease, hemochromatosis, and drug-induced liver disease, as determined by medical history, laboratory data, and imaging examinations; and 4 evidence of hepatocellular carcinoma, biliary tract cancer, or pancreatic cancer.

Clinical and Laboratory Evaluation

Body mass index was calculated as weight (kg) divided by the square of height (m^2). Laboratory evaluation included complete blood count, routine liver biochemistry (aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, and serum albumin), fasting lipids (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), and diabetes-related tests (fasting plasma glucose and hemoglobin A1c). Patients were diagnosed with type 2 diabetes mellitus (T2DM) based on meeting one of the following criteria: fasting plasma glucose ≥ 126 mg/dL, or 2-hour plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test, or diabetes symptoms and a random plasma glucose ≥ 200 mg/dL, or hemoglobin A1c $\geq 6.5\%$.

Statistical Analyses

The propensity score model was estimated using a logistic regression model that adjusted for patient characteristics, including age, sex, body mass index, and the prevalence of advanced fibrosis, which are known to be

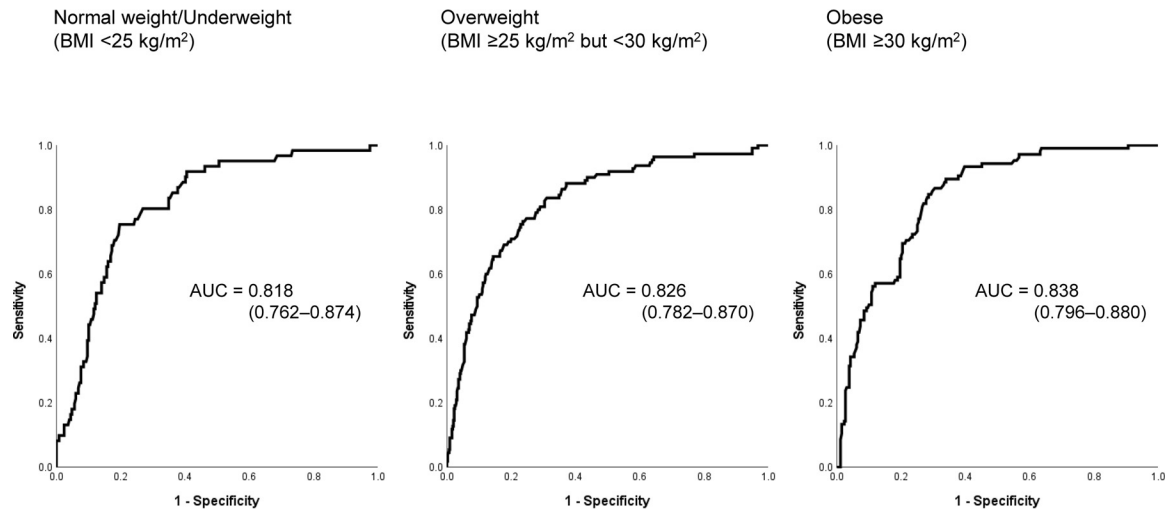
potential confounding factors that can affect the performance of non-invasive tests. One-to-one matching of patients was completed using nearest-neighbor matching without replacement, while the propensity score was matched using a caliper width of 0.2 logit of the standard deviation.

Supplementary Discussion

It is unclear why the diagnostic performance of the Fibrosis-4 (FIB-4) index is poor in patients with T2DM. Ito et al¹ attributed this to differences in liver enzyme expression between patients with and without T2DM. In our study, aspartate aminotransferase levels were nonsignificantly lower in patients with fibrosis stage 3–4 and T2DM (53 U/L) than in those with fibrosis stage 3–4 without T2DM (60 U/L) ([Supplementary Table 5](#)). Liver enzyme changes associated with the development of liver fibrosis might be less pronounced in patients with T2DM,^{1,2} which could affect the diagnostic performance of the FIB-4 index. By contrast, the NAFLD fibrosis score (NFS) is necessarily higher in patients with T2DM because the presence of diabetes is included in the NFS formula with a high coefficient value ([Supplementary Table 5](#)). This could cause the lower specificity of NFS in patients with T2DM, especially at a low cutoff value (-1.455) ([Table 3](#)). Therefore, the use of NFS in patients with T2DM would inevitably lead to a secondary screening test in many patients with medium-to-high risk scores, making it unsuitable for use in clinical diabetes practice.

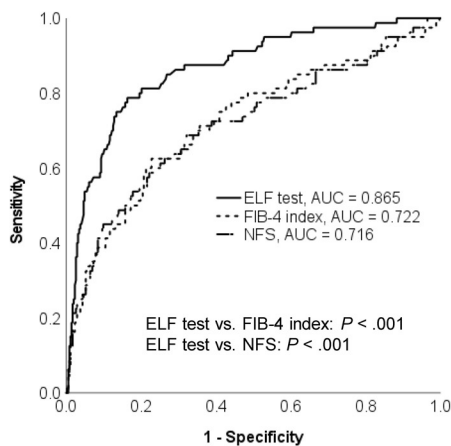
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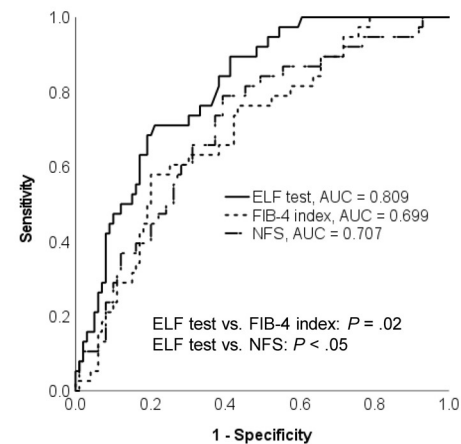


Supplementary Figure 1. Receiver-operating characteristic curve of the Enhanced Liver Fibrosis test for predicting advanced fibrosis (fibrosis stage 3–4) according to body mass index (BMI) categories. AUC, area under the curve.

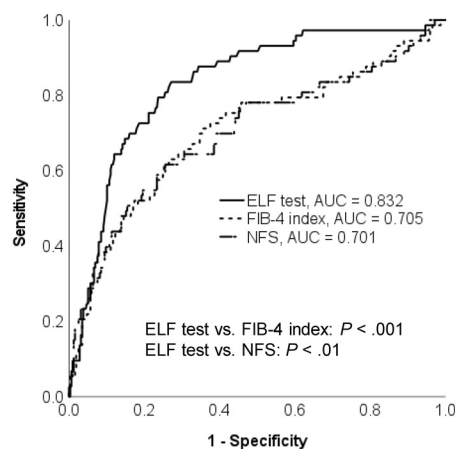
Males aged <65 years



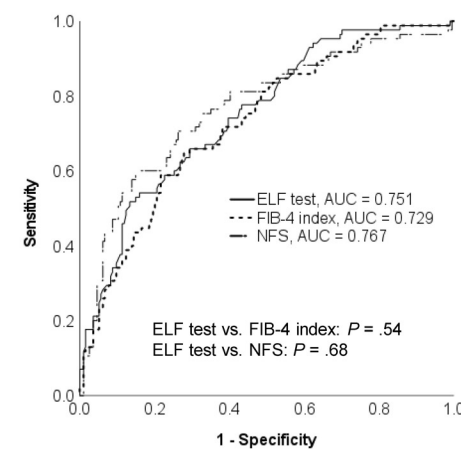
Males aged ≥65 years



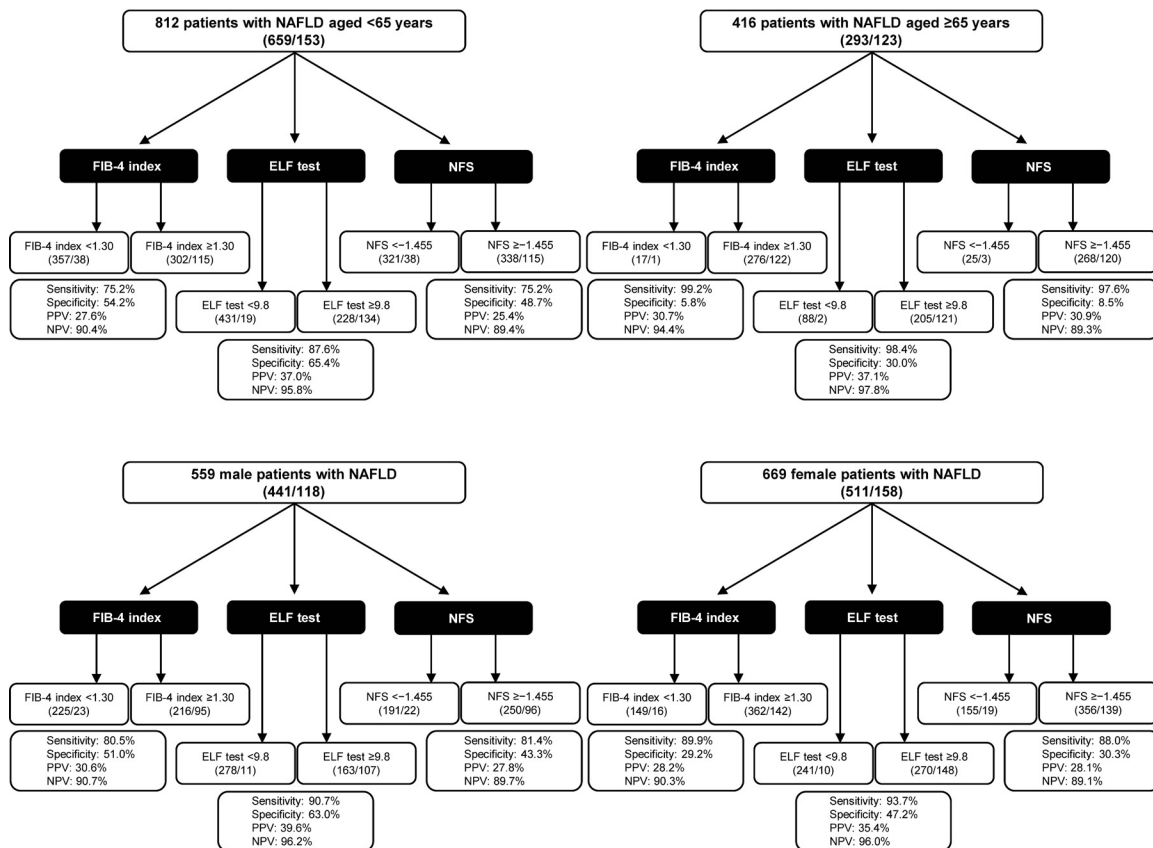
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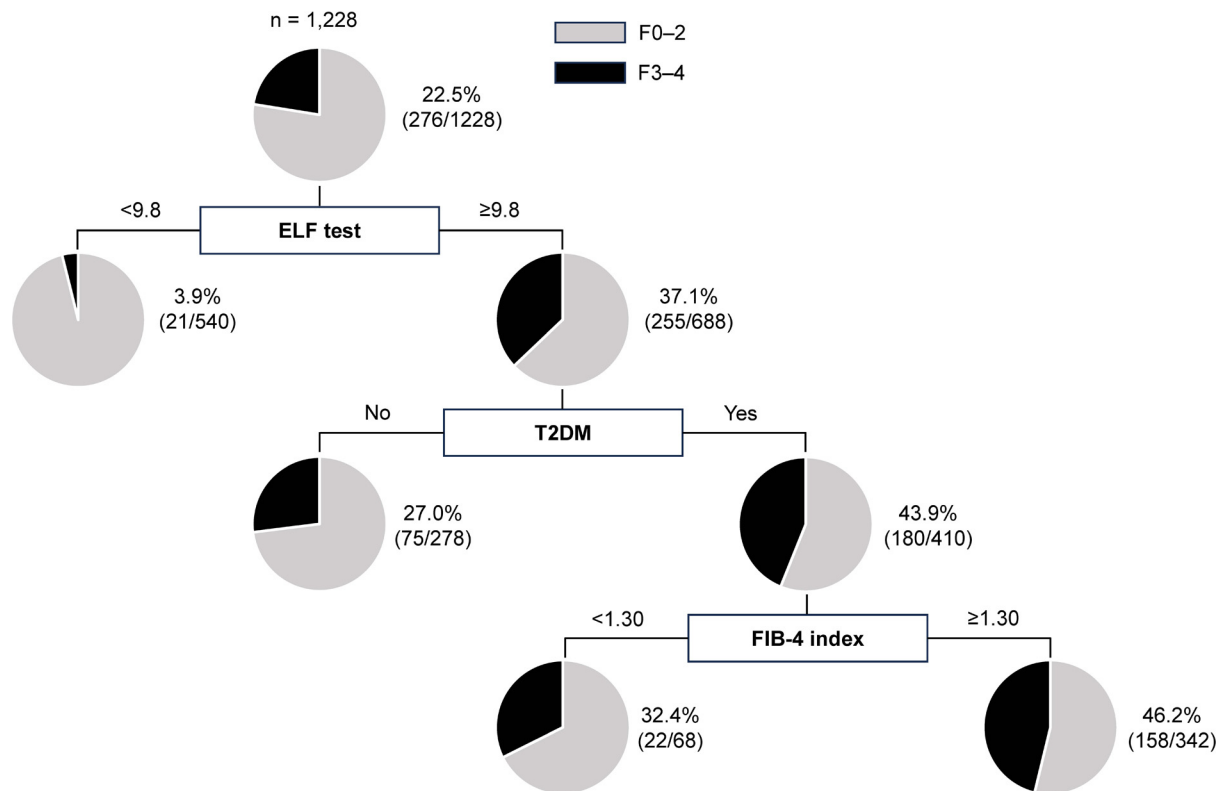
Females aged ≥65 years



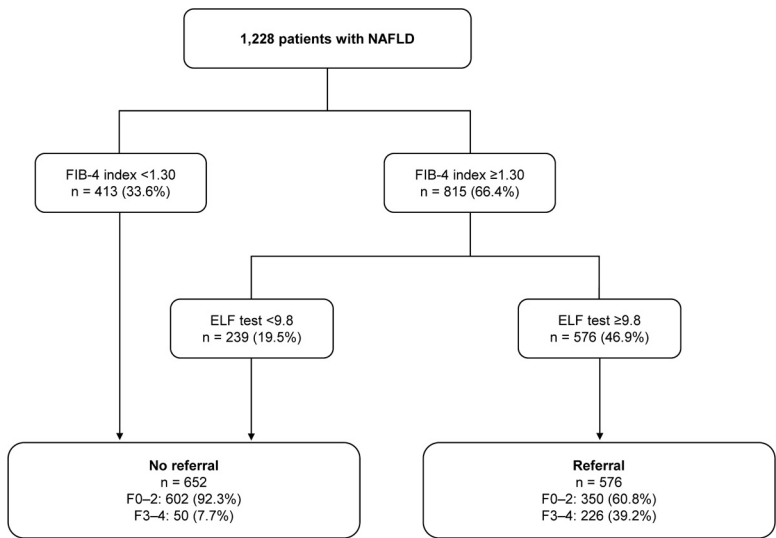
Supplementary Figure 2. Receiver-operating characteristic curves of the Fibrosis-4 (FIB-4) index, NAFLD fibrosis score (NFS), and Enhanced Liver Fibrosis (ELF) test for predicting advanced fibrosis (fibrosis stage 3–4) according to a combination of age and sex. AUC, area under the curve.



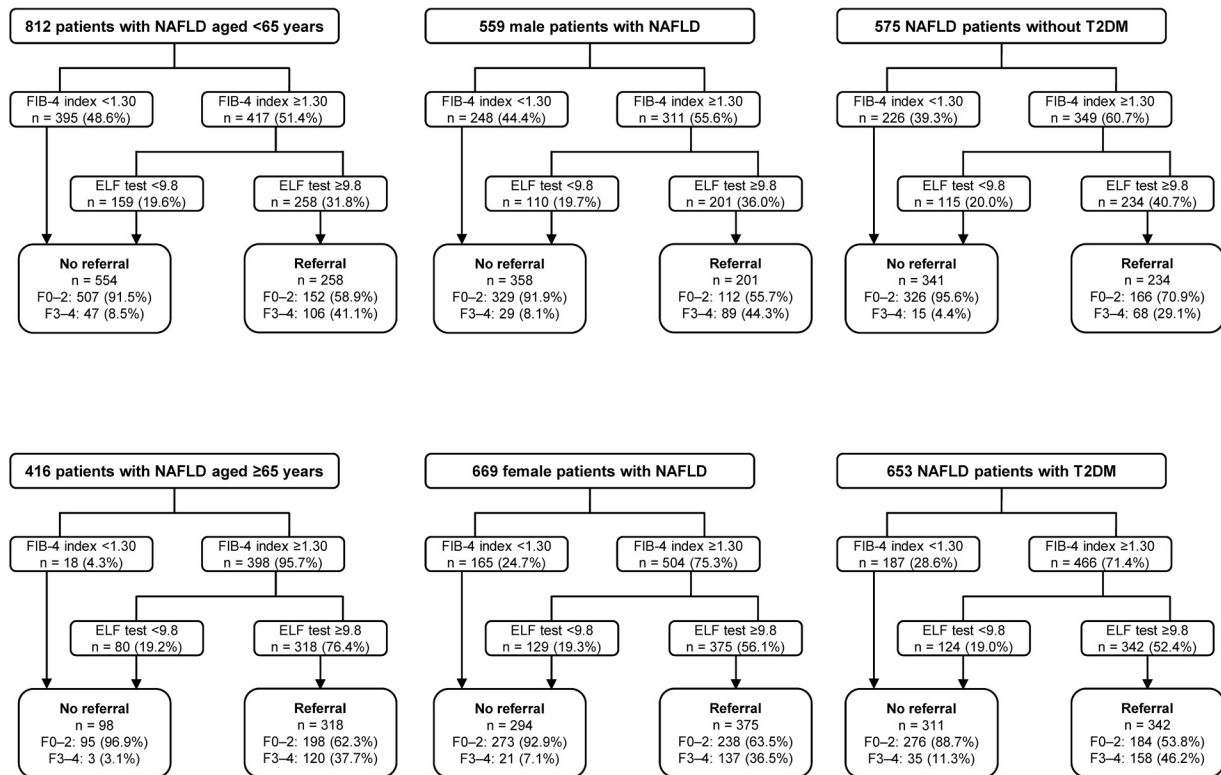
Supplementary Figure 3. Diagnostic accuracy of the Fibrosis-4 (FIB-4) index, NAFLD fibrosis score (NFS), and Enhanced Liver Fibrosis (ELF) test for predicting advanced fibrosis (fibrosis stage 3–4) at low cutoff values by age and sex. The numbers in parentheses are the number of patients without advanced fibrosis/number of patients with advanced fibrosis. NAFLD, nonalcoholic fatty liver disease; NPV, negative predictive value; PPV, positive predictive value.



Supplementary Figure 4. Decision tree algorithm for advanced fibrosis (fibrosis stage 3–4). Pie charts show the proportion of patients with and without advanced fibrosis. ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis-4; T2DM, type 2 diabetes mellitus.



Supplementary Figure 5. Diagnostic accuracy of the two-step strategy of the Fibrosis-4 (FIB-4) index followed by the Enhanced Liver Fibrosis (ELF) test for advanced fibrosis (fibrosis stage 3–4). NAFLD, nonalcoholic fatty liver disease.



Supplementary Figure 6. Diagnostic accuracy of the two-step strategy of the Fibrosis-4 (FIB-4) index followed by the Enhanced Liver Fibrosis (ELF) test for advanced fibrosis (fibrosis stage 3-4) by age, sex, and type 2 diabetes mellitus (T2DM). NAFLD, nonalcoholic fatty liver disease.

Supplementary Table 1. Univariate and Multivariate Logistic Regression Analysis of Factors Associated With Concordance Between the Enhanced Liver Fibrosis Test (Using a Low Cutoff of 9.8) and Liver Fibrosis (Fibrosis Stage 0–2 or 3–4)

Factor	Category	Univariate			Multivariate		
		OR	95% CI	P Value	OR	95% CI	P Value
Age	<65 y	2.27	1.78–2.89	<.001	2.13	1.66–2.74	<.001
Sex	Male	1.59	1.26–2.02	<.001	1.41	1.11–1.80	<.01
BMI	<25.0 kg/m ²	1.19	0.91–1.55	.20	1.02	0.78–1.35	.86
T2DM	Absence	0.98	0.78–1.23	.85	1.04	0.82–1.32	.75

BMI, body mass index; CI, confidence interval; OR, odds ratio; T2DM, type 2 diabetes mellitus.

Supplementary Table 2. Comparison of Characteristics of NAFLD Patients With and Without T2DM Before and After Propensity Score Matching

Factors	All Patients			After Propensity Score Matching		
	T2DM No (n = 575)	T2DM Yes (n = 653)	P Value	T2DM No (n = 479)	T2DM Yes (n = 479)	P Value
Age, y	57 (44–66)	61 (50–68)	<.001	60 (49–67)	59 (48–67)	.50
Males/female	271/304	288/365	.30	207/272	214/265	.70
Body weight, kg	70.0 (60.3–79.1)	72.0 (62.0–82.0)	.03	69.7 (60.6–79.4)	70.5 (61.6–81.0)	.39
BMI, kg/m ²	26.8 (24.3–29.9)	28.0 (25.5–31.2)	<.001	27.2 (24.8–30.2)	27.6 (25.1–30.5)	.28
Platelets (×10 ³ /mm ³)	207 (172–251)	200 (153–242)	.02	201 (167–245)	209 (167–251)	.18
AST, U/L	46 (33–69)	50 (34–72)	.12	46 (34–71)	50 (33–74)	.79
ALT, U/L	65 (40–99)	59 (38–91)	.14	63 (40–99)	61 (40–97)	.89
γ-GTP, U/L	55 (36–96)	66 (40–101)	<.01	54 (36–93)	64 (40–102)	.01
ALP, U/L	84 (67–110)	88 (70–111)	.25	86 (69–101)	89 (71–110)	.35
Albumin, g/dL	4.3 (4.1–4.5)	4.3 (4.0–4.5)	.08	4.3 (4.1–4.5)	4.3 (4.0–4.6)	.48
Total cholesterol, mg/dL	196 (176–219)	189 (167–216)	<.01	196 (176–218)	194 (171–224)	.38
LDL cholesterol, mg/dL	123 (103–146)	117 (96–138)	<.001	123 (104–144)	121 (99–145)	.32
HDL cholesterol, mg/dL	46 (40–55)	46 (39–55)	.58	46 (41–56)	46 (39–54)	.13
Triglyceride, mg/dL	133 (95–182)	138 (101–189)	.19	133 (95–174)	143 (101–192)	.03
Plasma glucose, mg/dL	98 (91–106)	125 (108–146)	<.001	99 (92–106)	124 (109–144)	<.001
HbA1c, %	5.6 (5.4–5.9)	6.7 (6.1–7.3)	<.001	5.7 (5.4–5.9)	6.7 (6.1–7.4)	<.001
FIB-4 index	1.63 (0.97–2.66)	2.04 (1.18–3.11)	<.001	1.83 (1.16–2.77)	1.75 (1.06–2.81)	.43
NFS	−1.311 (−2.364–0.341)	−0.193 (−1.200–0.725)	<.001	−1.077 (−1.921–0.122)	−0.590 (−1.391–0.448)	<.001
ELF test	9.7 (9.0–10.5)	10.2 (9.3–10.9)	<.001	9.8 (9.1–10.7)	9.9 (9.2–10.7)	.35
Fibrosis stage, 0/1/2/3/4	130/220/142/68/15	84/191/185/169/24	—	88/183/127/66/15	73/163/159/74/10	—
Fibrosis stage, 0–2/3–4	492/83	460/193	<.001	398/81	395/84	.86

Values are median (interquartile range) or n.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis-4; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; T2DM, type 2 diabetes mellitus; γ-GTP, gamma glutamyl transpeptidase.

Supplementary Table 3. Comparison of Characteristics of NAFLD Patients With Available Data on LSM by Transient Elastography With and Without T2DM Before and After Propensity Score Matching

Factor	All Patients			After Propensity Score Matching		
	T2DM No (n = 292)	T2DM Yes (n = 365)	P Value	T2DM No (n = 246)	T2DM Yes (n = 246)	P Value
Age, y	58 (46–67)	63 (52–68)	<.001	61 (51–69)	60 (49–67)	.30
Male/female	135/157	146/219	.11	101/145	103/143	.93
Body weight, kg	71.1 (60.7–81.4)	72.1 (61.9–83.2)	.70	70.3 (60.4–81.4)	71.5 (61.5–83.6)	.68
BMI, kg/m ²	27.4 (24.6–30.8)	28.4 (25.7–31.5)	<0.01	27.4 (24.5–31.0)	27.6 (25.2–31.0)	.35
Platelets ($\times 10^3/\text{mm}^3$)	203 (168–246)	192 (149–234)	.01	198 (163–237)	204 (161–242)	.38
AST, U/L	47 (34–67)	50 (35–71)	.22	47 (34–68)	49 (33–72)	.94
ALT, U/L	65 (42–97)	56 (38–88)	.02	62 (40–95)	57 (38–91)	.41
γ -GTP, U/L	57 (38–97)	64 (40–102)	.15	54 (37–97)	62 (39–100)	.20
ALP, U/L	84 (67–105)	85 (68–108)	.89	85 (67–106)	85 (66–105)	.81
Albumin, g/dL	4.2 (4.0–4.5)	4.2 (4.0–4.4)	.21	4.2 (4.0–4.4)	4.3 (4.0–4.5)	.58
Total cholesterol, mg/dL	196 (175–217)	184 (163–208)	<.001	195 (173–216)	186 (164–214)	.07
LDL cholesterol, mg/dL	122 (104–146)	114 (93–133)	<.001	122 (102–144)	117 (94–135)	.02
HDL cholesterol, mg/dL	47 (41–57)	47 (41–56)	.68	48 (42–58)	48 (41–56)	.56
Triglyceride, mg/dL	132 (98–178)	139 (105–187)	.23	126 (96–171)	144 (108–189)	.03
Plasma glucose, mg/dL	98 (93–105)	120 (106–139)	<.001	99 (93–106)	121 (106–138)	<.001
HbA1c, %	5.7 (5.5–6.0)	6.8 (6.2–7.4)	<.001	5.7 (5.5–6.0)	6.9 (6.3–7.4)	<.001
ELF test	9.8 (9.1–10.5)	10.3 (9.5–11.0)	<.001	9.9 (9.3–10.7)	10.0 (9.2–10.8)	.53
LSM, kPa	7.8 (6.0–11.3)	10.3 (7.3–16.6)	<.001	8.4 (6.2–12.0)	9.0 (6.8–13.4)	.05
Fibrosis stage, 0/1/2/3/4	57/110/73/42/10	39/103/99/106/18	—	42/86/66/42/10	36/82/71/47/10	—
Fibrosis stage, 0–2/3–4	240/52	241/124	<.001	194/52	189/57	.66

Values are median (interquartile range) or n.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ELF, Enhanced Liver Fibrosis; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LSM, liver stiffness measurement; NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; γ -GTP, gamma glutamyl transpeptidase.

Supplementary Table 4. The Diagnostic Performance of the ELF Test and LSM by Transient Elastography After Propensity Score Matching

	AUC (95% CI)	Cutoff Value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ELF test						
T2DM no	0.810 (0.749–0.870)	9.8	92.3	52.1	34.0	96.2
		11.3	38.5	90.7	52.6	84.6
T2DM yes	0.830 (0.776–0.884)	9.8	94.7	52.4	37.5	97.1
		11.3	43.9	91.0	59.5	84.3
LSM						
T2DM no	0.927 (0.886–0.967)	8.0 kPa	96.2	59.3	38.8	98.3
		12.0 kPa	88.5	87.1	64.8	96.6
T2DM yes	0.863 (0.808–0.919)	8.0 kPa	93.0	48.1	35.1	95.8
		12.0 kPa	75.4	83.6	58.1	91.9

AUC, area under the curve; CI, confidence interval; ELF, Enhanced Liver Fibrosis; LSM, liver stiffness measurement; NPV, negative predictive value; PPV, positive predictive value; T2DM, type 2 diabetes mellitus.

Supplementary Table 5. Comparison of Parameters Included in the FIB-4 Index and NFS Formula by Fibrosis Stage and T2DM Status After Propensity Score Matching

Factor	Fibrosis Stage 0–2			Fibrosis Stage 3–4		
	T2DM No (n = 398)	T2DM Yes (n = 395)	<i>P</i> Value	T2DM No (n = 81)	T2DM Yes (n = 84)	<i>P</i> Value
Age, y	60 (48 to 67)	58 (48 to 66)	.64	63 (54 to 71)	64 (50 to 69)	.50
BMI, kg/m ²	27.1 (24.7 to 30.1)	27.4 (25.1 to 30.0)	.32	27.6 (25.2 to 31.7)	28.8 (24.7 to 31.9)	.69
Platelets ($\times 10^3/\text{mm}^3$)	208 (174 to 247)	214 (181 to 258)	.15	161 (119 to 198)	163 (122 to 220)	.74
AST, U/L	45 (33 to 68)	48 (31 to 73)	.47	60 (40 to 84)	53 (38 to 74)	.21
ALT, U/L	63 (40 to 99)	63 (42 to 100)	.64	65 (39 to 95)	59 (39 to 86)	.53
Albumin, g/dL	4.3 (4.1 to 4.5)	4.3 (4.1 to 4.6)	.53	4.1 (3.8 to 4.4)	4.2 (3.8 to 4.5)	.76
FIB-4 index	1.71 (1.10 to 2.53)	1.59 (1.02 to 2.53)	.60	3.19 (1.93 to 4.20)	2.67 (1.73 to 4.38)	.41
NFS	−1.236 (−2.043 to −0.401)	−0.728 (−1.472 to 0.171)	<.001	0.249 (−1.096 to 1.145)	0.558 (−0.714 to 1.529)	.09
ELF test	9.7 (9.0 to 10.3)	9.7 (9.0 to 10.4)	.52	10.9 (10.3 to 11.5)	11.1 (10.5 to 11.7)	.26

Value are median (interquartile range).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ELF, Enhanced Liver Fibrosis; FIB-4, Fibrosis-4; NFS, NAFLD fibrosis score; T2DM, type 2 diabetes mellitus.